

Increased Incidence of Late Ventricular Potentials Following Prolonged Androgenic
Anabolic Steroid Use.

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ABSTRACT.

Objective The aim of this study was to examine markers of myocardial electrical stability using signal averaging electrocardiography (SAECG) to assess the presence of late ventricular potentials (LP) in very long term AAS users and compare these findings to an age and sex matched control group.

Design This was a retrospective study

Participants 10 long term AAS users (group A, AAS use 22 ± 3 yrs; age 39.9 ± 9 yrs) and 10 age matched controls (group C 42.1 ± 8 yrs).

Setting University of Glamorgan, human performance laboratory.

Intervention Both groups underwent SAECG analysis at rest and following an acute bout of exercise to volitional exhaustion. LP were analyzed using a 40Hz filter and were averaged over 200 beats.

Results: At rest and following an acute bout of exercise there was no difference in the mean values for any of the LP criteria. However, there was a higher incidence of abnormal LP in AAS users than in controls at rest ($p < 0.05$) and following an acute bout of exercise in all three criteria for LP ($p < 0.05$).

Conclusion: Prolonged AAS use may increase myocardial electrophysiological instability in certain individuals, both at rest and following exercise, placing AAS users at an increased risk of developing malignant tachyarrhythmias.

KEYWORDS – Late ventricular potentials; androgenic anabolic steroids (AAS), arrhythmias; sudden death.

INTRODUCTION.

Sudden death resulting from the clandestine non-therapeutic use of Androgenic Anabolic Steroids (AAS) is almost certainly under-reported in the medical and sports medicine literature.[1] While there are many reports in medical literature on the physiological effects of AAS in short to medium term users (<5 years [2]), the effects of more prolonged AAS use (>20 years) has received far less attention.[3] Furthermore, while the effects of AAS abuse on cardiac morphology have been studied[4, 5, 6] their effect on cardiac electro-physiology has not been extensively examined.

In vitro, AAS have been shown to be toxic to cultured myocytes[7, 8, 9] and cause mitochondrial disintegration.[9] One hypothesis is that reduced mitochondrial density in cardiac myocytes causes a decline in aerobic metabolism and eventually cell death and fibrosis.[9] An increase in fibrosis and connective collagen matrices may reduced ventricular compliance[7]. Increases in such non-contractile tissue disrupt electrical conduction in cardiac tissue[10, 11] which can be measured by surface electrodes during an electrocardiogram (ECG) using signal averaging (SAECG) to reduce signal to noise ratio. This fractionated electrical conduction is seen as a high frequency signal at the end of the QRS complex of the ECG and is termed a 'late potential' (LP). LP may decrease myocardial electrical stability and provide a re-entry mechanism for malignant ventricular tachycardias.[12, 13, 14]

Previous examination of endurance athletes has suggested that an acute bout of exercise reduces LP measures.[15, 16, 17, 18] There is a current lack of published data on long-term AAS use and LP. This study will examine the effect of long-term AAS use on LP both at rest and following an acute bout of exhaustive exercise.

METHOD

Subjects

Ethical approval for the study was obtained from the university ethical committee and all subjects involved, having read experimental details, provided written consent. AAS using participants were recruited from a database of subjects who had been involved in previous studies,[19] and from notices placed on bodybuilding web sites. Subsequently, 20 subjects were recruited to participate in the study. Subjects comprised of two age matched groups: long term (22 ± 3 yrs) steroid users ($n = 10$) and non steroid using resistance trained controls ($n = 10$; training = 18 ± 5 years). The steroid group included 3 previous international bodybuilding competitors and 2 current competitors, including 1 national champion and one senior national champion. No subjects reported any history of syncope, cardiovascular disease or bouts of tachyarrhythmia. Urinalysis was performed at an accredited International Olympic Committee (IOC) laboratory, Drug Control Centre, Kings College London, UK, to provide confirmation of AAS use and to eliminate potential positive samples.

Signal Averaged ECG

Subjects lay supine for 20 minutes. Following this, the subjects had ECG electrodes attached to their chest and underwent a standard resting ECG using commercially available equipment (CardioVit AT-60 Schiller, Sweden). This was followed by initiation of the LP program of the same machine. This program performs an algorithmic calculation of the 12 standard leads to produce the X, Y and Z vectors of the Frank lead system using the previously validated method of Simpson.[20] Signal acquisition limits were a minimum of 200 accepted QRS complexes using a bi-

directional Butterworth 40-250Hz band pass filter. LP filtering was accepted when noise levels were $\leq 0.3\mu\text{V}$. From the signal averaging process the following measurements were derived: high frequency QRS duration (HF QRS) in msec, root mean squared voltage of the last 40msec of the potential (RMS 40) in μV and duration of the low amplitude ($<40\mu\text{V}$) high frequency signal (LAHFd). Abnormal values were taken as HFQRS ≥ 114 msec, LAHDD ≥ 38 msec, RMS $\geq 20\mu\text{V}$. [11, 12] Following assessment of resting LP, subjects underwent an incremental treadmill exercise test, using the Bruce protocol, to volitional exhaustion. During the test, online gas analysis (Spiromed, Medgraphics Inc,) enabled determination of $\dot{V}O_{2MAX}$. Following the test, subjects lay supine for a second LP assessment using identical settings.

Statistical Analyses

Data were analysed using the SPSS 13.0 for Windows statistical package. Differences between groups were assessed using a two-way ANOVA. Incidence was calculated as a percentage of the sample, differences in observed frequencies of incidence were calculated by chi-square. Significance was set at the $p \leq 0.05$ level. All analyses were carried out using SPSS statistical software. Data are presented as Mean \pm Standard Deviations.

RESULTS.

Anthropometrics

There were no differences between controls or AAS users in age (42.1 ± 8 yrs v 39.9 ± 9 yrs respectively), height (174 ± 5.26 cm vs 171 ± 4.5 cm) or weight (82 ± 12.1 Kg vs 94.14 ± 15.15 Kg).

Signal Averaged ECG.

At rest, there was no significant difference between groups for filtered QRS duration, RMS 40 ms or LAHFd 40 μ V (Table 1).

Table 1. SAECG parameters for each group.

	<i>Control</i>	<i>AAS user</i>
<i>HFQRS (ms)</i>	89.27 ± 12.06	91.86 ± 18.37
<i>RMS40ms (μ V)</i>	73.39 ± 52.92	89.81 ± 75.77
<i>LAHFD (ms)</i>	16.00 ± 7.44	19.29 ± 7.59
<i>POSTHFQRS</i>	88.10 ± 10.21	99.29 ± 30.34
<i>POSTRMS40ms (μ V)</i>	74.41 ± 67.88	101.40 ± 86.86
<i>POSTLAHFd (ms)</i>	19.00 ± 4.24	25.29 ± 25.58
<i>Delta HFQRS *</i>	-1.20 ± 8.64	7.43 ± 22.39
<i>Delta RMS40ms *</i>	0.21 ± 29.46	11.59 ± 35.96
<i>DeltaLAHFd *</i>	2.70 ± 9.17	6.00 ± 26.22

Values are means \pm SD. * = Delta changes (calculated as post-pre 0. HFQRS = *high frequency QRS duration*, (>114ms abnormal) LAHFd = *low amplitude high frequency duration*,(>33ms abnormal) RMS40 = *root mean square voltage in the last 40 ms signal*.(<25 μ V abnormal)

In the control group, 1 subject (10%) showed an abnormal SAECG in one criteria (HFQRS > 114ms). The AAS users had 2 subjects (20%) with abnormal SAECG in one criteria, (HFQRS > 114ms) and 1 subject (10%) had 2 criteria for LP (RMS40ms < 20 μ V; HFQRS > 114ms; Table 2).

Table 2: Results of Chi-Square analyses for frequency of individual LP criteria.

	<i>Rest</i>			<i>Post-Exercise</i>		
	QRS	RMS 40	LaHFD	QRS	RMS 40	LaHFD
AAS	3*	1	0	3*	3*	3*
Control	1	0	0	0	0	0

HFQRS = high frequency QRS duration, (>114ms abnormal) LAHFd = low amplitude high frequency duration,(>33ms abnormal) RMS40 = root mean square voltage in the last 40 ms signal.(<25 μ V abnormal). * = p < 0.05 for frequency of abnormal criteria being higher in AAS. Note the three subjects with abnormal QRS at rest normalized after exercise, while the 3 subjects with abnormal post-exercise SAECG had appeared normal at rest.

Following exercise, no control subjects demonstrated any SAECG abnormality. There were 3 AAS users (30%), with an abnormal SAECG and all were abnormal in all three criteria (Table 2). The 3 AAS users with an abnormal resting SAECG improved their output following exercise, and the three subjects with an abnormal post exercise SAECG had previously demonstrated normal resting SAECG. The relative change in LP criteria was similar for both groups with no significance in the mean Delta QRS, RMS40ms or LAHFd 40 μ V . Whilst changes in the AAS group were larger than in the control group for all three criteria, the high standard deviations meant this did not reach significance. The chi-squared analyses demonstrated that at rest, there was a higher incidence of abnormal HFQRS duration in AAS compared to control (p < 0.05). Following exercise there was a significantly greater incidence of

all three abnormal SAECG measures in AAS compared to control ($p < 0.05$).

DISCUSSION.

The results of this study demonstrate a significant increase in the incidence of criteria for LP in long term AAS users compared to controls. LP are low amplitude, high frequency signals at the terminal portion of the QRS complex, and represent areas of fragmented and / or non-homogeneous electrical conduction through the myocardium.[12] While there are many case reports of AAS users suffering sudden cardiac death (SCD)[21, 22, 23] there is little direct evidence of the heart being a specific organ for AAS induced damage. Although AAS users often have increased cardiac mass and left ventricular hypertrophy, the link between AAS use and cardiac electrical instability remains unknown. The subjects in this study were long-term steroid users, and as such any AAS induced cardiac damage may be more pronounced.

The control group demonstrated an incidence of abnormal SAECG of 10%. Moroe et al.[17] found an incidence of 8.5% in normal population, and others have reported similar figures.[12, 24, 25] In addition, LP signals were improved in the control group following aerobic. This is in agreement with data on aerobically trained athletes undergoing aerobic exercise.[18] Moroe et al.[17] found a high (33%, 2 from 6) incidence of abnormal SAECG in weight lifters. This is in line with our data as 30% (3 from 10) of our AAS using subjects displayed abnormal SAECG in at least one of the LP criteria. However, it was unreported by Moroe et al.[17] whether their weight lifting subjects engaged in AAS administration.

Of the AAS subjects, 30% demonstrated worse criteria for LP following exercise. This is contrary to earlier research that suggests a bout of exercise improves SAECG

parameters, causing increased RMS energy and reduced filtered QRS duration.[18] This may be important as it indicates that long term AAS use may have caused a significant alteration in the electrophysiology of the myocardium. Furthermore since LP indicate a re-entry mechanism for arrhythmias[12, 26] and since the sympathetic stimulation required during an acute bout of exercise reduces ventricular refractoriness and fibrillation threshold,[27] these subjects will be at an increased risk of malignant tachyarrhythmias and potentially SCD following an acute bout of exercise.

It has been demonstrated that the areas of the myocardium where LP are present have normal membrane action potentials,[11] and the delayed activation is due to temporally asynchronous depolarisation of normal muscle bundles.[10] This delay is thought to be due either to diseased myocardial cells, or muscle bundles that have become fractionated due to intervening fibrosis or collagen tissue.[10, 11] Areas of fibrosis create functional unidirectional conduction blocks that force action potential waves around them, creating portions of the myocardium that depolarize later than its surrounding tissue.[13, 14, 26, 28]

AAS may increase the likelihood of such small fibrous and collagen conduction blocks. In vitro AAS have caused direct injury to cardiac tissue, resulting in mitochondrial destruction, and eventually myocyte death and fibrosis.[9] Also AAS have been shown to increase myocardial extra cellular collagen mass through enhanced lysyl oxidase activity.[7] In both cases it is likely these changes would happen throughout the myocardium. A small localized buildup may be sufficient to create fractionated conduction patterns. Furthermore this is perhaps more likely after very long term AAS use, as is the case here.

It is less clear why an acute bout of exercise increases LP criteria in certain subjects. It is possible that exercise-induced electro-physiological changes may uncover an area of functional block that was less evident during slower sinus rhythms. Pathological LVH *per se* has been shown to cause LP, due to changes in calcium permeability, both at rest[29] and following sudden changes in wall stress[30] as well as LP due to localised areas of fibrosis[31]. All of which could produce similar results to this study, furthermore all subjects that displayed worse SAECG following exercise had ECG predicted LVH ($SV1+RV5 > 25$ mm). If this is the case then it would indicate that these individuals may have pathological LVH.

LP provide a re-entry mechanism for malignant arrhythmias, and their presence may trigger a re-entry excitation wave. In an AAS using population, there are additional adverse effects on risk factors for adverse cardiac events. These include altered blood lipid, and lipoprotein levels[32], increased levels of aldosterone[33] increased hematocrit[34] and reduced dilation of coronary vascular beds[35]. This indicates that AAS users exhibiting LP may be at increased risk of re-entry based tachyarrhythmias irrespective of whether AAS use is responsible for the development of LP.

This investigation used subjects who had used AAS for over 20 years. It has previously been demonstrated that both moderate[36] and long term AAS use[37] may cause an increase in mortality. Therefore this study may underestimate the effect of AAS on myocardial electrophysiology since the present cohort may be self selecting as 'survivors' of very long term AAS use.

In conclusion the data here suggest that there was an increased incidence of abnormal SAECG measures in AAS users compared to controls. There was also an increase in

the incidence of post exercise LP in AAS users, and this may indicate a sub-group of users in whom long term AAS use exposes them to greater risk of SCD particularly following strenuous exercise.

TAKE HOME MESSAGE

Long term use of AAS may cause electrical instability within the myocardium, and such users may be at an even greater risk of malignant tachyarrhythmias immediately following exercise.

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